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Note

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α-C-Glycosides *via syn* Opening of 1,2-Anhydro Sugars with Organozinc Compounds in Toluene/*n*-Dibutyl Ether

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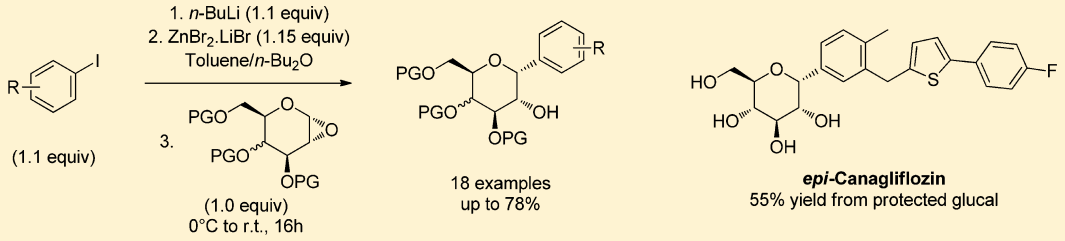
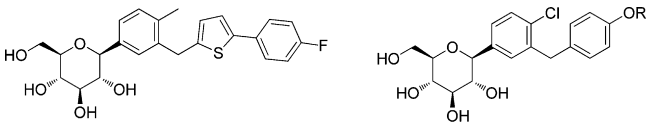
Supporting Information



ABSTRACT: The diastereoselective addition of organozinc species to 1,2-anhydro sugars in toluene/*n*-dibutyl ether solvent is reported. Compared to the existing methods, the reaction proceeds at 0 °C, and only a slight excess of nucleophile is required to achieve good yields. Scope was assessed with different *O*-protected glycals along with various nucleophiles (aryl, alkynyl). This methodology was applied to the synthesis of the α-anomer of canagliflozin.

The *C*-glycosides are ubiquitous in medicinal chemistry and have recently generated a profound interest as SGLT-2 inhibitors.[1] On top of the numerous compounds that are currently in both early[2] and late phase development for the treatment of type II diabetes (ertugliflozin,[3] tofogliflozin,[4] etc.), canagliflozin, dapagliflozin,[5] and empagliflozin[6] were recently approved in the United States and in Europe (Scheme 1).

Scheme 1. Approved SGLT-2 Inhibitors



Canagliflozin

R = Et: **Dapagliflozin**
R = 3-THF: **Empagliflozin**

In most cases, the stereoselective synthesis of these β-anomers relies on the addition of an organometallic species to an appropriately protected gluconolactone followed by silane-mediated reduction of the intermediate lactol.[7] We recently reported a highly diastereoselective *C*-glycosylation leading to the formation of canagliflozin.[8] This strategy consists in a substitution of a diarylzinc species on bromo sugar **1** in a toluene/*n*-dibutyl ether solvent mixture. Control experiments suggested the formation of an intermediate oxocarbenium via vicinal group participation of the pivaloyl ester at the 2-position (Scheme 2). With such a highly selective *C*-glycosylation strategy (over 98% β-selectivity) in hand, we then turned our attention toward a complementary methodology that would also give highly diastereoselective access to the corresponding α-anomers.

The addition of an organometallic species to a 1,2-anhydro sugar is a well-known method for the synthesis of *C*-glycosides. Interestingly, organocopper,[9] organomagnesium[10] and organotin[11] reagents react preferentially by an anti substitution mode. Conversely, the addition of boron, aluminum,[12] titanium,[13] zirconium,[14] and zinc[15] derivatives tend to yield predominantly the product of syn substitution (Scheme 3).

However, the synthesis of α-*C*-glycosides using organozinc reagents is currently hampered by the need to use a large excess of organometallic species[15b] or cryogenic temperatures and a large excess of an additional Lewis acid.[15c] Following our first investigation on the useful reactivity of organozinc reagents in *n*-dibutyl ether/toluene, we sought to extend the use of this solvent system to the ring opening of 1,2-anhydro sugars, aiming to develop a practical, scalable methodology that would obviate the need to use an excess of organometallic species, cryogenic temperature, or excess of Lewis acid.

We started this investigation by looking for a highly diastereoselective synthesis of glycal epoxides amenable to scale-up. This first reaction is key in the overall transformation as the diastereomeric ratio of the desired α-*C*-glycoside is directly linked to that of the starting epoxide. In 1989, Danishefsky et al. reported the diastereoselective epoxidation of benzyl-protected glucal by a freshly distilled dimethyldioxirane solution (DMDO).[16] This procedure (Method A) offers the advantage of using only a slight excess of DMDO and proceeds at 0 °C. Once the starting material is consumed, volatile byproducts are removed under reduced pressure to afford the desired glycal epoxide. Even though this strategy proved to be feasible on large scale,[17] it still involves the handling and the

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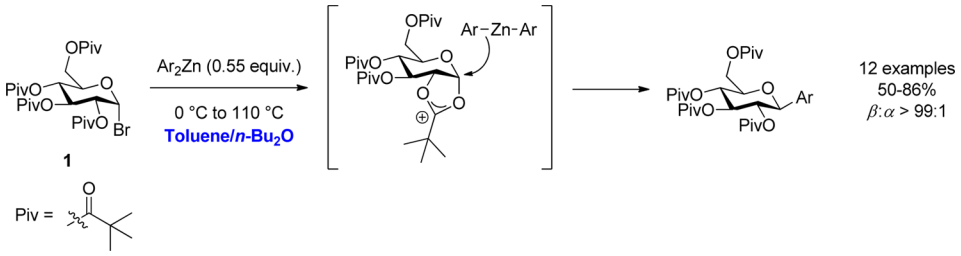
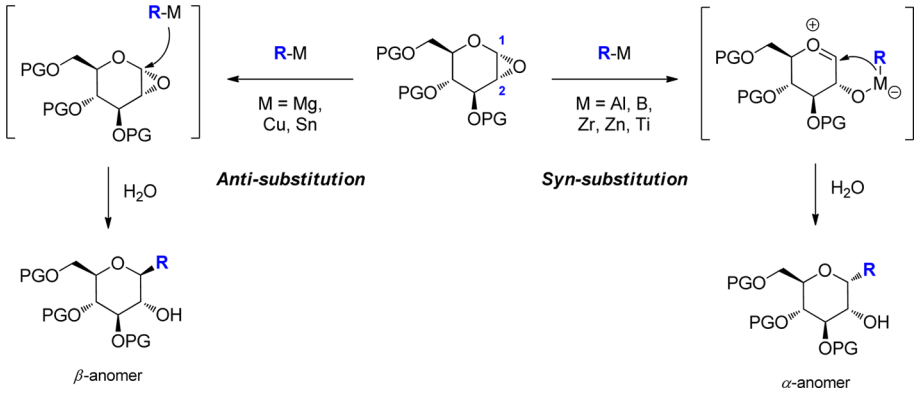
Scheme 2. Stereoselective Synthesis of β-*C*-Glycosides



Scheme 3. Stereodivergent Addition of Organometallic Species of 1,2-Anhydroglucals



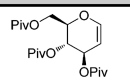
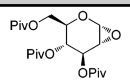
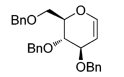
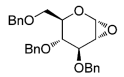
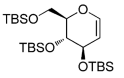
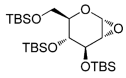
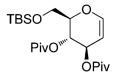
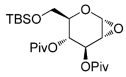
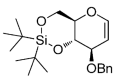
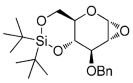
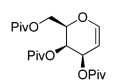
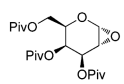
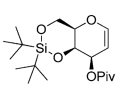
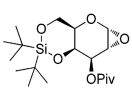
storage of volatile peroxide and a good diastereoselectivity can be achieved in some cases only with cryogenic temperatures, and extensive reaction time.[18] We were drawn to a recent report by Dondoni et al. about the direct epoxidation of glycals with an *in situ* generated DMDO.[19] This more practical approach consists of a biphasic system (dichloromethane/water) and oxone as the co-oxidant (Method B).

We first compared methods A and B in the case of pivaloyl-, benzyl-, and *tert*-butyldimethylsilyl-protected glucal (**2a**–**c**) and found very similar results both in terms of yields and diastereoselectivity (Table 1). For practical reasons, we chose method B and applied it to a small library of triprotected glucals and galactals. As previously observed, acetyl and benzoyl glucal epoxides were obtained in good yield but moderate anomeric ratio. Orthogonally protected glucals **2d** and **2e** all gave good yield and excellent diastereoselectivity. The α-epoxide was the sole product detectable by NMR in the case of the galactal derivatives **2f** and **2g**.

With a robust epoxidation procedure in hand, we then turned our attention to the coupling reaction in the presence of organozinc species. Unlike most of its analogues, glucal epoxide **3a** turned out to be a bench-stable white solid and was chosen as initial substrate for our studies, in conjunction with *p*-benzyloxyiodobenzene. After lithiation of the iodoarene with a slight excess of *n*-butyllithium in toluene, various amounts of $ZnBr_2$·LiBr in *n*-dibutyl ether[20] were added to the reaction mixture at 0 °C to test the influence of the resulting organometallic species. The reaction mixture was then slowly warmed up to room temperature and left stirring overnight (Table 2).

In the presence of the aryl zinc bromide species, the desired α-*C*-glycoside **4aa** was formed (Table 2, entry 1), as indicated by NMR analysis, with special attention to the coupling constant of the anomeric proton[12] (J_{1-2} = 3.7 Hz). A moderate yield of 48% was achieved when using 0.55 equiv of zinc bromide (Table 2, entry 2). Further decreasing the zinc amount, presumably allowing the formation of a zincate species, did not improve the final yield.[21] The aryllithium species did not lead to the formation of the desired product, probably due to a degradation of the electrophile (Table 2, entries 3 and 4).

Table 1. Glycal Epoxidation by DMDO

Glycal		Method	Anhydro glycal		Yield	α:β[a]
2a		A	**3a**		98%	7:1
		B			97%	10:1
2b		A	**3b**		99%[b]	10:1
		B			96%	10:1
2c		A	**3c**		96%	20:1
		B			99%	>20:1
2d		B	**3d**		83%	14:1
2e		B	**3e**		67%	10:1
2f		B	**3f**		95%	>20:1
2g		B	**3g**		88%	>20:1

Method A: DMDO (0.05 M – 1.2 equiv) in acetone, DCM, 0 °C, 30 min. Method B: Oxone (2.5–3.0 equiv), acetone (10–15 equiv), $NaHCO_3$ sat., DCM, 0 °C. [a]Diastereomeric ratio determined by NMR. [b]See ref 18.

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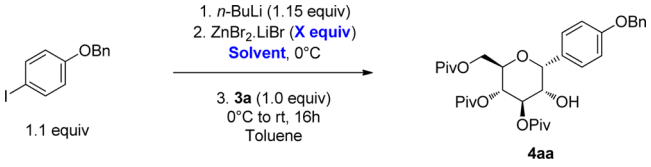
Table 2. Epoxide Opening Study



Entry	$ZnBr_2$·LiBr	Solvent for $ZnBr_2$·LiBr	Additive	Formed reagent	Isolated Yield
1	1.15 equiv	*n*-Bu_2O	-	ArZnBr	72%
2	0.55 equiv	*n*-Bu_2O	-	Ar_2Zn	48%
3	0.4 equiv	*n*-Bu_2O	-	Ar_3ZnLi	48%
4	0	*n*-Bu_2O	-	ArLi	traces
5	0.55 equiv.	*n*-Bu_2O	TFA (2.0 equiv)	ArZnTFA	46%
6	1.15 equiv.	THF	-	ArZnBr	0%

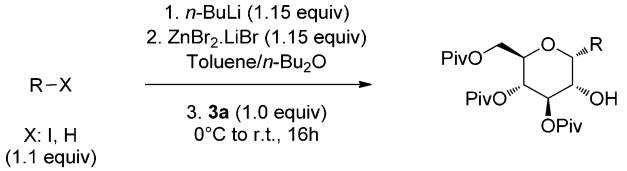
In situ formation of the ArZnTFA species by adding 2 equiv of trifluoroacetic acid as described by Xue[15b] afforded a moderate yield of 46% (Table 2, entry 5). Finally, no trace of the desired product was detected when introducing zinc bromide as a solution in THF rather than *n*-dibutyl ether, thus stressing the importance of the solvent mixture for the reactivity of organozinc species (Table 2, entry 6). In the end, a slight excess of aryl zinc bromide gave the best yield and these conditions were selected as baseline for the investigation of the reaction scope.

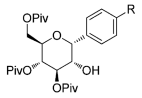
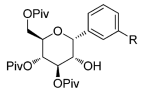
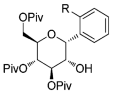
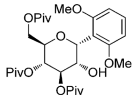
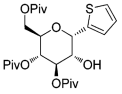
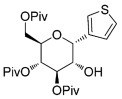
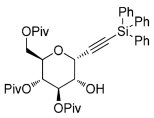
We then studied a broad range of nucleophiles for the opening of epoxide **3a** (Table 3). Electron-withdrawing groups in the *para* position give moderate to low yields (Table 3, entry 1, R = Cl, F). Iodobenzene afforded the desired α-*C*-glucoside in a moderate 52% yield (Table 3, entry 1, R = H). Good to moderate yields can be obtained for meta substituents with the electron-withdrawing groups being favored in this case (Table 3, entry 2). *Ortho*-substituents are tolerated although yields are lower probably due to steric bulk around the reactive center (Table 3, entries 3−4). In the case of 1,3-dimethoxybenzene, the organozinc species was obtained by ortho-lithiation followed by transmetalation. Two- and three-substituted five-membered heterocycles can also be added to epoxide **3a** to afford the corresponding α-*C*-glucosides (Table 3, entries 5 and 6). Finally, α-alkynyl-glucoside **4al** was isolated in a 53% yield after a deprotonation/transmetalation/epoxide opening sequence (Table 3, entry 7).[22]

Protected epoxides **3a−g** were then reacted with aryl zinc bromide species generated from 4-benzyloxyiodobenzene (Table 4). The type of protecting group does not have a major impact on the outcome of the reaction and the corresponding α-*C*-glucoside was isolated in 70−73% yield (Table 4 − entries 1−3). Orthogonally protected glucals **3d−e** were ring opened in good yields allowing potential selective deprotection and subsequent functionalization (Table 4, entries 4 and 5). Galactal epoxides **3f−g** afforded the corresponding α-*C*-galactosides in good yields (Table 4, entries 6 and 7).

With this methodology in hand, we attempted to develop a one-pot synthesis of the α-anomer of canagliflozin, a key impurity in the drug substance, starting from glucal **2a** (Scheme 4). After epoxidation of glycal **2a** and solvent switch to toluene, the freshly prepared aryl zinc derivative was coupled with **3a**.

Table 3. Screening of Various Nucleophiles



Entry	Nucleophile	Product		R	Isolated yield
			4aa	OBn	72%
1			**4ab**	Cl	49%
			4ac	F	14%
			4ad	H	52%
2			**4ae**	OBn	37%
			4af	Cl	64%
3			**4ag**	Me	59%
			4ah	OMe	36%
4			**4ai**		33%
5			**4aj**		58%
6			**4ak**		62%
7			**4al**		53%

After complete conversion, workup and solvent switch to methanol, the pivaloyl protecting groups were removed in the presence of sodium methoxide in refluxing methanol.[23] The desired α-anomer of canagliflozin **5** was thereafter isolated in a 55% yield over three steps as a single diastereomer.

In conclusion, we have developed a moderately efficient, highly stereospecific and straightforward access to α-aryl glycosides under noncryogenic conditions and in the presence of a stoichiometric amount of nucleophile. Reaction conditions involving the unusually effective toluene/*n*-dibutyl ether solvent mixture are compatible with large-scale synthesis. Finally, we extended this strategy to the α-anomer of canagliflozin in 55% yield over three steps without isolation of the intermediates.

EXPERIMENTAL SECTION

Instrumentation and Materials. ^1H and ^{13}C NMR spectra were recorded at 360 and 90 MHz respectively in $CDCl_3$ or DMSO-d_6 solutions. HRMS data were obtained via LC-MS (EI, TOF) or GC-MS (electrospray). TLC analyses were performed on commercial glass plates bearing a 0.25 mm layer of silica gel 60F254. Silica gel was used for column chromatography. Unless otherwise noted, materials obtained from commercial suppliers were used as received.

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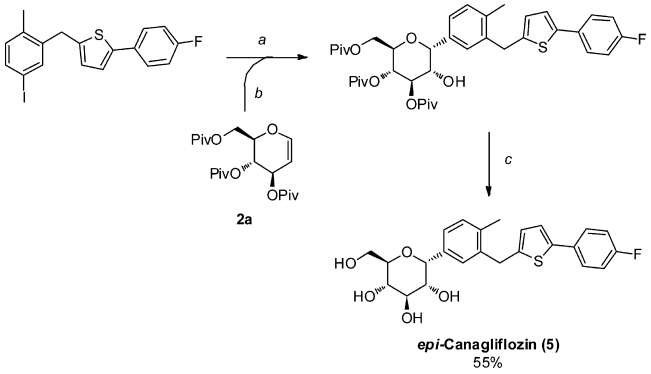
Table 4. Reaction of Various Glycal Epoxides

Entry	Electrophile	Product	Isolated Yield
1	**3a**	**4aa**	72%
2	**3b**	**4ba**	70%
3	**3c**	**4ca**	73%
4	**3d**	**4da**	75%
5	**3e**	**4ea**	61%
6	**3f**	**4fa**	59%
7	**3g**	**4ga**	74%

Scheme 4. One-Pot Deprotection Towards *epi*-Canagliflozin[a]



[a]Reaction conditions: (a) *n*-BuLi (1.15 equiv), $ZnBr_2$·LiBr in *n*-Bu_2O (1.15 equiv), toluene, 0 °C; (b) Oxone (3.0 equiv), acetone (10 equiv), $NaHCO_3$ aq., DCM, H_2O, 0 °C; (c) MeONa (1.0 equiv), MeOH, reflux.

Glycal Synthesis. Glucals **2b** and **2c** are commercially available and were used as such. Glucals **2e** and **2f** were synthesized according to the literature.[24]

*1,5-Anhydro-2-deoxy-3,4,6-tris-O-(2,2-dimethylpropanoyl)-D-arabino-hex-1-enitol (**2a**).* A round-bottom flask was charged with 2,3,4,6-tetra-*O*-pivaloyl-α-D-glucopyranosyl bromide (40.0 g, 69.0 mmol) and filled up with THF (200 mL), water (200 mL), and acetic acid (200 mL). The resulting mixture was cooled to 0 °C. Zinc dust (36.0 g, 550 mmol) was added in portions to the reaction mixture which was maintained at 0 °C for 30 min after the end of addition. The mixture was warmed up to 25 °C within 3 h and stirred for 16 h. The crude mixture was filtered with Dicalite and extracted with DCM. The organic layer was washed with an aqueous solution of NH_4Cl (23% w/w) and a saturated solution of $NaHCO_3$. The pH was adjusted to ca. 10 with an aqueous solution of NaOH (40% w/w). The organic layer was dried with Na_2SO_4. The solvent was removed under reduced pressure leading to **2a** obtained as a white solid (26.8 g, 97%). R_f 0.62 (70:30 95:5 heptane/ethyl acetate). The spectroscopic data were in full agreement with those reported.[24a] ^{1}H NMR ($CDCl_3$, 360 MHz) δ 6.46 (dd, *J* = 6.0, 2.5 Hz, 1H), 5.34−5.30 (m, 1H), 5.30−5.25 (m, 1H), 4.82 (dd, *J* = 6.0, 3.3 Hz, 1H), 4.34 (dd, *J* = 11.5, 5.5 Hz, 1H), 4.31−4.25 (m, 1H), 4.22 (dd, *J* = 11.5, 2.5 Hz, 1H), 1.24 (s, 9H), 1.19 (s, 9H), 1.19 (s, 9H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 178.1, 177.8, 176.6, 145.6, 99.1, 74.1, 67.5, 66.7, 61.3, 38.9, 38.7, 38.7, 27.1, 27.0, 27.0.

*1,5-Anhydro-6-O-[tert-butyl(dimethyl)silyl]-2-deoxy-3,4-bis-O-(2,2-dimethylpropano-yl)-D-arabino-hex-1-enitol (**2d**).* Monosilylated D-glucal[25] (126 g, 483 mmol) was dissolved in DCM (110 mL), and pyridine (780 mL, 20 equiv) and DMAP (11.8 g, 0.2 equiv) were added to the resulting mixture which was cooled down to 0 °C. After dropwise addition of pivaloyl chloride (239 mL, 4 equiv), the mixture was allowed to warm up to room temperature and further stirred for 24 h. After quench with ice-cold water, the mixture was extracted with ethyl acetate and washed with saturated brine. The organic layer was dried over sodium sulfate, filtered, and concentrated under vacuum to give the crude product. Glucal **2d** was isolated as a pure compound after flash chromatography on silica gel (100:1 to 20:1 petroleum ether/ethyl acetate). R_f 0.3 (95:5 heptane/ethyl acetate). ^{1}H NMR ($CDCl_3$, 360 MHz) δ 6.47 (dd, *J* = 6.2, 1.5 Hz, 1H), 5.32−5.27 (m, 1H), 5.25 (dd, *J* = 7.7, 5.9 Hz, 1H), 4.77 (dd, *J* = 6.2, 2.9 Hz, 1H), 4.14−4.07 (m, 1H), 3.84 (dd, *J* = 11.3, 5.9 Hz, 1H), 3.77 (dd, *J* = 11.3, 2.9 Hz, 1H), 1.19 (s, 9H), 1.18 (s, 9H), 0.90 (s, 9H), 0.07 (s, 3H), 0.07 (s, 3H). ^{13}C NMR ($CDCl_3$, 90 MHz) δ 177.9, 176.5, 145.8, 98.6, 77.2, 67.8, 67.0, 61.6, 38.7, 27.0, 27.0, 25.8, −5.3. HRMS calcd for $C_{22}H_{41}O_6Si$ $[M + H]^+$ 429.2672, found 429.2662.

*2,6-Anhydro-5-deoxy-1,3-O-(di-tert-butylsilanylidene)-4-O-(2,2-dimethylpropanoyl)-D-arabino-hex-5-enitol (**2g**).* Silyl ether formation was accomplished starting from D-galactal according to the literature.[26] 2,6-Anhydro-5-deoxy-1,3-*O*-(di-*tert*-butylsilanylidene)-D-*arabino*-hex-5-enitol (503 mg, 1.76 mmol) was dissolved in acetone (4L/mol) under inert atmosphere (N_2), and the mixture was cooled down to 0 °C. Pivaloyl chloride (258 μL, 2.11 mmol, 1.5 equiv), triethylamine (330 μL, 2.37 mmol, 1.5 equiv), and dimethylaminopyridine (21 mg, 0.18 mmol, 0.1 equiv) were added dropwise to the mixture, and the solution was stirred at room temperature. After 16 h, the reaction was quenched with a solution of NH_4Cl (23 w%). The aqueous layer was extracted three times with ethyl acetate. All organic layers were combined and washed with a solution of NaOH (40 w%), water, dried over Na_2SO_4, filtered, and finally put under reduced pressure to remove volatile materials. Purification on silica gel by flash column chromatography (95:5 heptane/ethyl acetate) afforded the desired product as a white solid (456 mg, 70%). R_f 0.42 (95:5 heptane/ethyl acetate). ^{1}H NMR ($CDCl_3$, 360 MHz) δ 6.44 (dd, *J* = 6.2, 1.8 Hz, 1H), 5.25−5.20 (m, 1H), 4.82−4.78 (m, 1H), 4.66 (dt, *J* = 6.2, 1.8 Hz, 1H), 4.27 (ddd, *J* = 12.4, 5.5, 1.8 Hz, 2H), 3.89 (s, 1H), 1.24 (s, 9H), 1.03 (s, 9H), 1.02 (s, 9H). ^{13}C NMR ($CDCl_3$, 90 MHz) δ 178.3, 145.4, 98.8, 73.0, 67.3, 67.1, 65.1, 38.8, 27.7, 27.2, 26.9, 23.3, 20.8. HRMS calcd for $C_{19}H_{35}O_5Si$ $[M + H]^+$ 371.2248, found 371.2248.

Zinc Bromide Lithium Bromide Solution in *n*-Dibutyl Ether. Inside a glovebox, a 50 mL Schlenk tube with magnetic stirrer was charged with solid zinc bromide (7.11 g, 31.6 mmol), lithium bromide (2.74 g, 31.6 mmol), and *n*-dibutyl ether (30 mL). The resulting mixture was stirred overnight inside the glovebox and used as such for the next step.

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General Procedure for the Synthesis of Glycal Epoxides. *Method A.* According to the literature, a round-bottom flask was charged with glycal (1.0 equiv) and dichloromethane (10 L/mol) and cooled to 0 °C with an ice bath. An ice-cooled solution of DMDO (1.2 equiv) was then added, and the resulting mixture was stirred for 1 h before being warmed up to room temperature. The volatile materials were finally removed under reduced pressure to yield the desired glycal epoxide.

Method B.[19] A reactor was charged with the glycal (1.0 equiv) and dichloromethane (5 L/mol). Acetone (10−15 equiv). Thereafter, saturated sodium bicarbonate (10 L/mol) was added to the mixture, and the reactor was cooled to 0 °C. A solution of potassium monopersulfate (2.5 to 3.0 equiv) in water (7 L/mol) was added dropwise, and the reaction mixture was stirred at 0 °C for 1 to 4 h after the end of addition. After phase separation, the aqueous layer was washed once with DCM. The organic layers were combined and washed three times with a saturated solution of $NaHCO_3$, once with water, dried over Na_2SO_4, and evaporated *in vacuo*. The resulting glycal epoxide was used as such without further purification. Diastereomeric ratios were determined by NMR analysis of the crude mixture.

General Procedure for the syn-Addition of Organozinc Species to Glycal Epoxides. A 25 mL Schlenk tube with magnetic agitation under N_2 atmosphere was charged with iodoarene (1.10 equiv) and toluene (8 mL/g) and cooled to 0 °C using an ice-bath. *n*-Butyllithium (1.15 equiv, 25% w/w in heptane) was added dropwise over 5 min. After 30 min, $ZnBr_2$−LiBr (1.15 equiv, 32% w/w in *n*-Bu_2O) was added dropwise over 5 min at 0 °C. After 30 min, a solution of 1,2-anhydro-glucal (1.0 equiv) in toluene (1 mL/g) was added dropwise over 5 min to the reaction mixture, which was then left to warm up to room temperature overnight. After 14h, the reaction was quenched with an ammonium chloride saturated solution, and the organic phase was extracted twice with ethyl acetate. Volatile materials were removed under reduced pressure, and the desired *C*-glycoside was isolated as a pure compound after flash chromatography on silica gel.

*(1R)-1,5-Anhydro-1-[4-(benzyloxy)phenyl]-3,4,6-tris-O-(2,2-dimethylpropanoyl)-D-glucitol (**4aa**). Epoxide **3a** Synthesis.* General procedure starting from D-glucal **2a** (2.00 g, 5.02 mmol) and potassium monopersulfate (9.26 g, 15.1 mmol) in water (35.1 mL), acetone (5.5 mL), saturated sodium bicarbonate (50.2 mL), and dichloromethane (25.1 mL). **3a** was obtained as a white solid as a 10:1 mixture of two diastereomers (2.01 g, 97%). R_f 0.05 (70:30 heptane/ethyl acetate).

Epoxide Opening. General procedure using 4-benzyloxyiodobenzene (823 mg, 2.65 mmol), *n*-BuLi (1.00 mL, 25% w/w in heptane, 2.77 mmol), $ZnBr_2$−LiBr (2.50 mL, 32% w/w in *n*-Bu_2O, 2.77 mmol), and 1,2-anhydro-glucal **3a** (1.00 g, 2.41 mmol). Purification by flash chromatography (95:5 heptane/ethyl acetate) afforded **4aa** as a white solid (1.03 g, 72%). R_f 0.3 (95:5 heptane/ethyl acetate). ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.54−7.30 (m, 7H), 6.99 (d, J = 8.4 Hz, 2H), 5.36 (t, J = 6.6 Hz, 1H), 5.11 (d, J = 3.7 Hz, 1H), 5.08 (s, 2H), 5.01 (t, J = 6.6 Hz, 1H), 4.44 (dd, J = 12.1, 7.7 Hz, 1H), 4.11−4.03 (m, 2H), 3.99−3.91 (m 1H), 2.57−2.31 (br s, 1H), 1.26 (s, 9H), 1.20 (s, 18H). ^{13}C NMR ($CDCl_3$, 90 MHz) δ 178.0, 177.8, 176.7, 158.4, 136.8, 129.0, 128.9, 128.6, 128.0, 127.5, 114.8, 72.9, 71.9, 71.6, 70.5, 70.0, 67.6, 61.3, 38.9, 38.8, 27.1, 27.0. HRMS calcd for $C_{34}H_{50}NO_9$ $[M + NH_4]^+$ 616.3480, found 616.3483.

*(1R)-1,5-Anhydro-1-(4-chlorophenyl)-3,4,6-tris-O-(2,2-dimethylpropanoyl)-D-glucitol (**4ab**).* General procedure using 4-chloroiodobenzene (320 mg, 1.33 mmol), *n*-BuLi (500 μL, 25% w/w in heptane, 1.38 mmol), $ZnBr_2$−LiBr (1.20 mL, 32% w/w in *n*-Bu_2O, 1.38 mmol), and 1,2-anhydro-glucal **3a** (500 mg, 1.21 mmol). Purification by flash chromatography (95:5 heptane/ethyl acetate) afforded **4ab** as a white solid (310 mg, 49%). R_f 0.3 (95:5 heptane/ethyl acetate). ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.49 (d, J = 8.8 Hz, 2H), 7.34 (d, J = 8.8 Hz, 2H), 5.26 (d, J = 6.2, 5.9 Hz, 1H), 5.08 (d, J = 3.3 Hz, 1H), 4.97 (t, J = 5.5 Hz, 1H), 4.56 (dd, J = 11.7, 8.1 Hz, 1H), 4.07−3.95 (m, 3H), 2.59 (d, J = 8.1 Hz, 1H), 1.26 (s, 9H), 1.20 (s, 9H), 1.18 (s, 9H). ^{13}C NMR ($CDCl_3$, 90 MHz) δ 178.0, 177.5, 176.6, 135.5, 133.7, 128.7, 128.5, 72.6, 72.1, 71.0, 70.0, 67.3, 60.9, 38.9, 38.8, 27.1, 27.0, 27.0. HRMS calcd for $C_{27}H_{43}NO_8Cl$ $[M + NH_4]^+$ 544.2677, found 544.2679.

*(1R)-1,5-Anhydro-3,4,6-tris-O-(2,2-dimethylpropanoyl)-1-(4-fluorophenyl)-D-glucitol (**4ac**).* General procedure using 4-fluoroiodobenzene (153 μL, 1.33 mmol), *n*-BuLi (500 μL, 25% w/w in heptane, 1.38 mmol), $ZnBr_2$−LiBr (1.20 mL, 32% w/w in *n*-Bu_2O, 1.38 mmol), and 1,2-anhydro-glucal **3a** (500 mg, 1.21 mmol). Purification by flash chromatography (95:5 heptane/ethyl acetate) afforded **4ac** as a white solid (90 mg, 15%). R_f 0.3 (95:5 heptane/ethyl acetate). ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.52 (dd, J = 8.8, 5.1 Hz, 2H), 7.07 (t, J = 8.8 Hz, 2H), 5.28 (dd, J = 6.2, 5.9 Hz, 1H), 5.10 (d, J = 3.3 Hz, 1H), 4.98 (t, J = 5.5 Hz, 1H), 4.57 (dd, J = 11.7, 8.1 Hz, 1H), 4.09−3.97 (m, 3H), 2.50 (d, J = 8.1 Hz, 1H), 1.29 (s, 9H), 1.20 (s, 9H), 1.19 (s, 9H). ^{13}C NMR ($CDCl_3$, 90 MHz) δ 178.0, 177.5, 176.6, 162.3 (d, J = 246.6 Hz), 132.7 (d, J = 3.5 Hz), 129.2 (d, J = 7.6 Hz), 128.4, 127.9, 127.4, 115.3 (d, J = 21.5 Hz), 72.7, 72.1, 71.1, 70.0, 67.3, 60.9, 38.9, 38.8, 38.8, 27.2, 27.1, 27.1. HRMS calcd for $C_{27}H_{43}FNO_8$ $[M + NH_4]^+$ 528.2967, found 528.2967.

*(1R)-1,5-Anhydro-3,4,6-tris-O-(2,2-dimethylpropanoyl)-1-phenyl-D-glucitol (**4ad**).* General procedure using iodobenzene (270 mg, 1.33 mmol), *n*-BuLi (500 μL, 25% w/w in heptane, 1.38 mmol), $ZnBr_2$−LiBr (1.20 mL, 32% w/w in *n*-Bu_2O, 1.38 mmol), and 1,2-anhydro-glucal **3a** (500 mg, 1.21 mmol). Purification by flash chromatography (95:5 heptane/ethyl acetate) afforded **4ad** as a white solid (310 mg, 52%). R_f 0.3 (95:5 heptane/ethyl acetate). ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.55 (d, J = 7.7 Hz, 2H), 7.42−7.35 (m, 2H), 7.35−7.29 (m, 1H), 5.33 (dd, J = 6.2, 5.9 Hz, 1H), 5.14 (d, J = 3.7 Hz, 1H), 5.00 (dd, J = 5.9, 5.5 Hz, 1H), 4.51 (dd, J = 11.7, 7.7 Hz, 1H), 4.12−3.98 (m, 3H), 2.51 (d, J = 6.6 Hz, 1H), 1.29 (s, 9H), 1.20 (s, 9H), 1.19 (s, 9H). ^{13}C NMR ($CDCl_3$, 90 MHz) δ 178.0, 177.6, 176.7, 136.8, 128.4, 127.9, 127.4, 72.8, 72.4, 71.3, 70.2, 67.5, 61.1, 38.9, 38.8, 27.1, 27.1, 27.0. HRMS calcd for $C_{27}H_{44}NO_8$ $[M + NH_4]^+$ 510.3061, found 510.3064.

*(1R)-1,5-Anhydro-1-[3-(benzyloxy)phenyl]-3,4,6-tris-O-(2,2-dimethylpropanoyl)-D-glucitol (**4ae**).* General procedure using 3-benzyloxyiodobenzene (411 mg, 1.33 mmol), *n*-BuLi (500 μL, 25% w/w in heptane, 1.38 mmol), $ZnBr_2$−LiBr (1.20 mL, 32% w/w in *n*-Bu_2O, 1.38 mmol), and 1,2-anhydro-glucal **3a** (500 mg, 1.21 mmol). Purification by flash chromatography (90:10 heptane/ethyl acetate) afforded **4ae** as colorless oil (270 mg, 37%). R_f 0.3 (95:5 heptane/ethyl acetate). ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.47−7.28 (m, 6H), 7.20−7.18 (br s, 1H), 7.14 (d, J = 7.7 Hz, 1H), 6.93 (dd, J = 8.0, 2.2 Hz, 1H), 5.30 (t, J = 5.9 Hz, 1H), 5.10 (d, J = 3.3 Hz, 1H), 5.08 (s, 2H), 5.01 (t, J = 5.5 Hz, 1H), 4.55−4.47 (m, 1H), 4.12−4.00 (m, 3H), 2.45 (d, J = 7.0 Hz, 1H), 1.27 (s, 9H), 1.21 (s, 9H), 1.20 (s, 9H). ^{13}C NMR ($CDCl_3$, 90 MHz) δ 178.1, 177.7, 176.6, 158.9, 138.5, 136.9, 129.5, 128.5, 128.0, 127.5, 119.6, 114.2, 113.9, 72.5, 71.2, 70.2, 70.0, 67.4, 61.1, 38.9, 38.8, 27.1, 27.0. HRMS calcd for $C_{34}H_{50}NO_9$ $[M + NH_4]^+$ 616.3480, found 616.3479.

*(1R)-1,5-Anhydro-1-(3-chlorophenyl)-3,4,6-tris-O-(2,2-dimethylpropanoyl)-D-glucitol (**4af**).* General procedure using 3-chloroiodobenzene (320 mg, 1.33 mmol), *n*-BuLi (500 μL, 25% w/w in heptane, 1.38 mmol), $ZnBr_2$−LiBr (1.20 mL, 32% w/w in *n*-Bu_2O, 1.38 mmol), and 1,2-anhydro-glucal **3a** (500 mg, 1.21 mmol). Purification by flash chromatography (95:5 heptane/ethyl acetate) afforded **4af** as a white solid (410 mg, 64%). R_f 0.3 (95:5 heptane/ethyl acetate). ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.51 (s, 1H), 7.46−7.38 (m, 1H), 7.33−7.24 (m, 2H), 5.24 (dd, J = 5.9, 5.5 Hz, 1H), 5.07 (d, J = 2.9 Hz, 1H), 4.96 (dd, J = 5.5, 5.2 Hz, 1H), 4.60 (dd, J = 12.8, 9.1 Hz, 1H), 4.08−3.98 (m, 3H), 2.62 (d, J = 8.4 Hz, 1H), 1.26 (s, 9H), 1.20 (s, 9H), 1.19 (s, 9H). ^{13}C NMR ($CDCl_3$, 90 MHz) δ 178.1, 177.3, 176.6, 139.1, 134.4, 129.6, 128.0, 127.5, 125.2, 72.9, 71.8, 70.8, 69.7, 67.3, 60.8, 38.9, 38.8, 27.1, 27.0. HRMS calcd for $C_{27}H_{43}NO_8Cl$ $[M + NH_4]^+$ 544.2677, found 544.2679.

*(1R)-1,5-Anhydro-3,4,6-tris-O-(2,2-dimethylpropanoyl)-1-(2-methylphenyl)-D-glucitol (**4ag**).* General procedure using 2-methyliodobenzene (580 mg, 2.65 mmol), *n*-BuLi (1.0 mL, 25% w/w in heptane, 2.77 mmol), $ZnBr_2$−LiBr (2.50 mL, 32% w/w in *n*-Bu_2O, 2.77 mmol), and 1,2-anhydro-glucal **3a** (1.00 g, 2.41 mmol). Purification by flash chromatography (95:5 heptane/ethyl acetate) afforded **4ag** as a colorless oil (720 mg, 59%). R_f 0.3 (95:5 heptane/

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ethyl acetate). ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.62−7.57 (m, 1H), 7.25−7.15 (m, 3H), 5.33 (t, J = 5.0 Hz, 1H), 5.27 (d, J = 2.6 Hz, 1H), 4.98−4.94 (m, 1H), 4.74−4.66 (m, 1H), 4.14−4.05 (m, 2H), 3.95−3.87 (br s, 1H), 2.33 (s, 3H), 1.29 (s, 9H), 1.24 (s, 9H), 1.11 (s, 9H). ^{13}C NMR ($CDCl_3$, 90 MHz) δ 178.1, 177.2, 176.7, 135.4, 134.8, 130.6, 127.8, 127.5, 125.7, 73.1, 71.0, 69.4, 68.3, 67.1, 60.6, 38.9, 38.8, 38.7, 27.1, 27.1, 27.0, 19.3. HRMS calcd for $C_{28}H_{43}O_8$ $[M + H]^+$ 507.2952, found 507.2951.

*(1R)-1,5-Anhydro-3,4,6-tris-O-(2,2-dimethylpropanoyl)-1-(2-methoxyphenyl)-D-glucitol (**4ah**).* General procedure using 2-iodoanisole (627 mg, 2.65 mmol), n-BuLi (1.0 mL, 25% w/w in heptane, 2.77 mmol), $ZnBr_2$−LiBr (2.50 mL, 32% w/w in n-Bu_2O, 2.77 mmol), and 1,2-anhydro-glucal **3a** (1.00 g, 2.41 mmol). Purification by flash chromatography (95:5 heptane/ethyl acetate) afforded **4ah** as a colorless oil (455 mg, 36%). R_f 0.3 (95:5 heptane/ethyl acetate). ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.51 (dd, J = 7.7, 1.1 Hz, 1H), 7.28 (td, J = 8.1, 1.8 Hz, 1H), 6.99 (td, J = 7.7, 0.7 Hz, 1H), 6.86 (dd, J = 8.4, 0.7 Hz, 1H), 5.35 (d, J = 1.5 Hz, 1H), 5.18−5.14 (m, 1H), 4.99−4.95 (m, 1H), 4.68 (dd, J = 10.6, 7.0 Hz, 1H), 4.30−4.19 (m, 2H), 3.96−3.93 (m, 1H), 3.80 (s, 3H), 1.30 (s, 9H), 1.25 (s, 9H), 1.15 (s, 9H). ^{13}C NMR ($CDCl_3$, 90 MHz) δ 178.1, 176.7, 176.6, 155.5, 128.6, 127.7, 125.7, 120.5, 110.0, 73.7, 70.3, 67.2, 67.1, 67.0, 60.8, 55.2, 38.8, 38.8, 38.7, 27.1. HRMS calcd for $C_{28}H_{43}O_9$ $[M + H]^+$ 523.2902, found 523.2905.

*(1R)-1,5-Anhydro-1-(2,6-dimethoxyphenyl)-3,4,6-tris-O-(2,2-dimethylpropanoyl)-D-glucitol (**4ai**).* General procedure using 1,3-dimethoxybenzene (374 mg, 2.65 mmol), s-BuLi (2.1 mL, 1.4 M in cyclohexane, 2.90 mmol), $ZnBr_2$−LiBr (2.50 mL, 32% w/w in n-Bu_2O, 2.77 mmol), and 1,2-anhydro-glucal **3a** (1.00 g, 2.41 mmol). Purification by flash chromatography (95:5 heptane/ethyl acetate) afforded **4ai** as a colorless oil (440 mg, 33%). R_f 0.15 (95:5 heptane/ethyl acetate). ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.28 (t, J = 8.4 Hz, 1H), 7.17 (d, J = 8.4 Hz, 2H), 5.74 (d, J = 5.1 Hz, 1H), 5.55 (t, J = 6.2 Hz, 1H), 4.98 (dd, J = 6.6, 6.2 Hz, 1H), 4.30 (dd, J = 11.7, 7.7 Hz, 1H), 4.18 (dd, J = 11.7, 4.0 Hz, 1H), 3.92−3.85 (m, 8H), 1.28 (s, 9H), 1.22 (s, 9H), 1.09 (s, 9H). ^{13}C NMR ($CDCl_3$, 90 MHz) δ 178.1, 177.8, 176.9, 158.7, 130.0, 113.8, 105.1, 73.0, 72.1, 70.7, 68.3, 67.8, 61.9, 56.2, 38.8, 38.7, 27.1, 27.1, 27.0. HRMS calcd for $C_{29}H_{45}O_{10}$ $[M + H]^+$ 553.3007, found 553.3005.

*(1S)-1,5-Anhydro-3,4,6-tris-O-(2,2-dimethylpropanoyl)-1-thiophen-2-yl-D-glucitol (**4aj**).* General procedure using 2-iodothiophene (143 μL, 1.33 mmol), n-BuLi (500 μL, 25% w/w in heptane, 1.38 mmol), $ZnBr_2$−LiBr (1.20 mL, 32% w/w in n-Bu_2O, 1.38 mmol), and 1,2-anhydro-glucal **3a** (500 mg, 1.21 mmol). Purification by flash chromatography (95:5 heptane/ethyl acetate) afforded **4aj** as a white solid (350 mg, 58%). R_f 0.3 (95:5 heptane/ethyl acetate). ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.37 (dd, J = 5.1, 1.1 Hz, 1H), 7.34 (dt, J = 3.7, 1.1 Hz, 1H), 7.06 (dd, J = 5.1, 3.7 Hz, 1H), 5.45 (d, J = 5.5 Hz, 1H), 5.42 (t, J = 8.8 Hz, 1H), 5.09 (t, J = 8.8 Hz, 1H), 4.26−4.15 (m, 2H), 4.09 (dd, J = 12.2, 2.2 Hz, 1H), 3.99−3.92 (m, 1H), 2.79−2.59 (br s, 1H), 1.23 (s, 18H), 1.16 (s, 9H). ^{13}C NMR ($CDCl_3$, 90 MHz) δ 179.0, 178.1, 176.6, 138.2, 127.8, 126.8, 126.4, 73.1, 73.0, 71.4, 70.9, 67.7, 61.9, 39.0, 38.9, 38.8, 27.2, 27.1, 27.0. HRMS calcd for $C_{25}H_{42}NO_8S$ $[M + NH_4]^+$ 516.2626, found 516.2634.

*(1R)-1,5-Anhydro-3,4,6-tris-O-(2,2-dimethylpropanoyl)-1-thiophen-3-yl-D-glucitol (**4ak**).* General procedure using 3-iodothiophene (143 μL, 1.33 mmol), n-BuLi (400 μL, 25% w/w in heptane, 1.38 mmol), $ZnBr_2$−LiBr (1.02 mL, 32% w/w in n-Bu_2O, 1.38 mmol), and 1,2-anhydro-glucal **3a** (400 mg, 1.21 mmol). Purification by flash chromatography (95:5 heptane/ethyl acetate) afforded **4ak** as a white solid (375 mg, 62%). R_f 0.3 (95:5 heptane/ethyl acetate). ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.66−7.63 (m, 1H), 7.36 (dd, J = 4.8, 3.0 Hz, 1H), 7.23 (dd, J = 5.1, 1.1 Hz, 1H), 5.41 (t, J = 8.4 Hz, 1H), 5.25 (d, J = 5.1 Hz, 1H), 5.05 (t, J = 8.4 Hz, 1H), 4.24−4.14 (m, 2H), 4.08 (dd, J = 12.2, 2.2 Hz, 1H), 3.80−3.73 (m, 1H), 2.66−2.44 (br s, 1H), 1.23 (s, 9H), 1.23 (s, 9H), 1.15 (s, 9H). ^{13}C NMR ($CDCl_3$, 90 MHz) δ 178.1, 178.0, 176.7, 136.7, 127.7, 125.9, 124.3, 72.7, 72.7, 71.2, 71.1, 68.0, 62.0, 38.9, 38.8, 38.8, 27.2, 27.0. HRMS calcd for $C_{25}H_{42}NO_8S$ $[M + NH_4]^+$ 516.2626, found 516.2618.

*(1R)-1,5-Anhydro-3,4,6-tris-O-(2,2-dimethylpropanoyl)-1-[(triphenylsilyl)ethynyl]-D-glucitol (**4al**).* General procedure using (triphenylsilyl)acetylene (385 mg, 1.33 mmol), n-BuLi (500 μL, 25% w/w in heptane, 1.38 mmol), $ZnBr_2$−LiBr (1.20 mL, 32% w/w in n-Bu_2O, 1.38 mmol), and 1,2-anhydro-glucal **3a** (500 mg, 1.21 mmol). Purification by flash chromatography (95:5 heptane/ethyl acetate) afforded **4al** as a white solid (450 mg, 53%). R_f 0.3 (95:5 heptane/ethyl acetate). ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.71−7.65 (m, 6H), 7.50−7.39 (m, 9H), 5.37 (t, J = 9.7 Hz, 1H), 5.08 (t, J = 9.7 Hz, 1H), 4.97 (d, J = 6.2 Hz, 1H), 4.25−4.15 (m, 2H), 4.09 (dd, J = 12.1, 5.1 Hz, 1H), 3.87−3.80 (m, 1H), 2.51−2.25 (br s, 1H), 1.22 (s, 9H), 1.19 (s, 9H), 1.17 (s, 9H). ^{13}C NMR ($CDCl_3$, 90 MHz) δ 179.4, 178.0, 176.5, 135.5, 132.5, 130.2, 128.2, 74.4, 71.8, 70.8, 69.5, 66.9, 61.9, 38.9, 38.8, 38.8, 27.1, 27.0, 27.0. HRMS calcd for $C_{41}H_{54}NO_8Si$ $[M + NH_4]^+$ 716.3613, found 716.3618.

*(1R)-1,5-Anhydro-3,4,6-tri-O-benzyl-1-[4-(benzyloxy)phenyl]-D-glucitol (**4ba**). Epoxide Opening.* General procedure using 4-benzyloxyiodobenzene (789 mg, 2.54 mmol), n-BuLi (960 μL, 25% w/w in heptane, 2.66 mmol), $ZnBr_2$−LiBr (2.40 mL, 32% w/w in n-Bu_2O, 2.66 mmol), and 1,2-anhydro-glucal **3b** (1.00 g, 2.31 mmol). Purification by flash chromatography (95:5 heptane/ethyl acetate) afforded **4ba** as a colorless oil (1.00g, 70%). R_f 0.3 (95:5 heptane/ethyl acetate). ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.46−7.23 (m, 22H), 6.96 (d, J = 8.8 Hz, 2H), 5.07 (s, 2H), 4.92 (s, 1H), 4.66−4.57 (m, 4H), 4.57 (d, J = 12.4 Hz, 1H), 4.51 (d, J = 12.4 Hz, 1H), 4.33−4.28 (m, 1H), 3.98−3.94 (m, 1H), 3.89 (dd, J = 10.3, 6.6 Hz, 1H), 3.85−3.77 (m, 2H), 3.74−3.71 (m, 1H). ^{13}C NMR ($CDCl_3$, 90 MHz) δ 158.0, 138.2, 137.8, 137.3, 137.1, 133.3, 128.6, 128.5, 128.5, 128.4, 128.2, 128.0, 128.0, 127.9, 127.9, 127.6, 127.6, 127.4, 114.5, 76.1, 74.7, 73.6, 73.2, 72.8, 72.2, 71.1, 70.3, 70.0, 67.8. HRMS calcd for $C_{40}H_{44}NO_6$ $[M + NH_4]^+$ 634.3169, found 634.3164.

*(1R)-1,5-Anhydro-1-[4-(benzyloxy)phenyl]-3,4,6-tris-O-[tert-butyl(dimethyl)silyl]-D-glucitol (**4ca**). Epoxide **3c** Synthesis.* General procedure starting from **2c** (1.00 g, 2.05 mmol) and potassium monopersulfate (3.14 g, 5.11 mmol) in water (14.3 mL), acetone (1.5 mL), saturated sodium bicarbonate (20.5 mL), and dichloromethane (10.2 mL). **3c** was obtained as a colorless oil as a single diastereomer (>20:1 by NMR analysis) (1.02 g, 99%). R_f 0.05 (70:30 heptane/ethyl acetate).

Epoxide Opening. General procedure using 4-benzyloxyiodobenzene (676 mg, 2.18 mmol), n-BuLi (822 μL, 25% w/w in heptane, 2.28 mmol), $ZnBr_2$−LiBr (2.10 mL, 32% w/w in n-Bu_2O, 2.28 mmol), and 1,2-anhydro-glucal **3c** (1.00 g, 1.98 mmol). Purification by flash chromatography (95:5 heptane/ethyl acetate) afforded **4ca** as a colorless oil (1.00g, 73%). R_f 0.3 (95:5 heptane/ethyl acetate). ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.46−7.29 (m, 7H), 6.97 (d, J = 7.7 Hz, 2H), 5.07 (s, 2H), 4.87 (s, 1H), 4.18−4.11 (m, 1H), 4.05−3.99 (m, 2H), 3.96−3.90 (m 2H), 0.95 (s, 9H), 0.95 (s, 9H), 0.90 (s, 9H), 0.17−0.14 (s, 12H), 0.05 (s, 6H). ^{13}C NMR ($CDCl_3$, 90 MHz) δ 158.0, 137.2, 133.3, 128.5, 127.9, 127.8, 127.4, 114.4, 80.7, 72.2, 70.8, 70.0, 68.8, 61.3, 25.9, 25.8, 18.2, 18.0, −4.9, −5.0, −5.0, −5.1, −5.3, −5.4. HRMS calcd for $C_{37}H_{68}NO_6Si_3$ $[M + NH_4]^+$ 706.4349, found 706.4350.

*(1R)-1,5-Anhydro-1-[4-(benzyloxy)phenyl]-6-O-[tert-butyl(dimethyl)silyl]-3,4-bis-O-(2,2-dimethylpropanoyl)-D-glucitol (**4da**). Epoxide **3d** Synthesis.* General procedure starting from **2d** (258 mg, 0.60 mmol) and potassium monopersulfate (1.11 g, 1.81 mmol) in water (4.2 mL), acetone (663 μL, 9.0 mmol), saturated sodium bicarbonate (6.0 mL), and dichloromethane (3.0 mL). **3d** was obtained as a white solid as a 15:1 mixture of two diastereomers (223 mg, 83%). R_f 0.23 (70:30 heptane/ethyl acetate).

Epoxide Opening. General procedure using 4-benzyloxyiodobenzene (171 mg, 0.55 mmol), n-BuLi (210 μL, 25% w/w in heptane, 0.58 mmol), $ZnBr_2$−LiBr (0.52 mL, 32% w/w in n-Bu_2O, 0.58 mmol), and 1,2-anhydro-glucal **3d** (223 mg, 0.50 mmol). Purification by flash chromatography (95:5 heptane/ethyl acetate) afforded **4da** as a colorless oil (235 mg, 75%). R_f 0.3 (95:5 heptane/ethyl acetate). ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.53 (d, J = 8.8 Hz, 2H), 7.47−7.30 (m, 5H), 7.00 (d, J = 8.8 Hz, 2H), 5.33 (t, J = 6.6 Hz, 1H), 5.11−5.03 (m, 4H), 4.05 (dd, J = 7.0, 4.4 Hz, 1H), 3.84−3.76 (m, 2H), 3.73−3.69

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(m, 1H), 1.25 (s, 9H), 1.19 (s, 9H), 0.89 (s, 9H). ^{13}C NMR ($CDCl_3$, 90 MHz) δ 177.9, 176.6, 158.3, 137.0, 129.4, 128.9, 128.6, 127.9, 127.5, 114.8, 74.7, 72.3, 70.9, 70.0, 68.0, 61.7, 38.8, 38.7, 38.7, 27.1, 27.1, 25.8, 18.2, −5.4. HRMS calcd for $C_{35}H_{56}NO_8Si$ $[M + NH_4]^+$ 646.3764, found 646.3770.

*(1R)-1,5-Anhydro-3-O-benzyl-1-[4-(benzyloxy)phenyl]-4,6-O-(di-tert-butylsilanylidene)-D-glucitol (**4ea**). Epoxide **3e** Synthesis.* General procedure starting from **2e** (240 mg, 0.64 mmol) and potassium monopersulfate (1.18 g, 1.91 mmol) in water (4.4 mL), acetone (703 μL, 9.56 mmol), saturated sodium bicarbonate (6.4 mL), and dichloromethane (3.2 mL). **3e** was obtained as a yellow oil as a 10:1 mixture of two diastereomers (168 mg, 67%). R_f 0.05 (95:5 Heptane/Ethyl acetate).

Epoxide Opening. General procedure using 4-benzyloxyiodobenzene (378 mg, 1.09 mmol), *n*-BuLi (460 μL, 25% w/w in heptane, 1.27 mmol), $ZnBr_2$−LiBr (1.10 mL, 32% w/w in *n*-Bu_2O, 1.27 mmol), and 1,2-anhydro-glucal **3e** (435 mg, 1.11 mmol). Purification by flash chromatography (95:5 heptane/ethyl acetate) afforded **4ea** as a colorless oil (392 mg, 61%). R_f 0.3 (95:5 heptane/ethyl acetate). ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.53−7.32 (m, 12H), 6.96 (d, J = 8.8 Hz, 2H), 5.14−5.08 (m, 2H), 5.09 (s, 2H), 4.81 (d, J = 11.3 Hz, 1H), 4.12−4.03 (m, 3H), 3.91−3.84 (m, 2H), 3.57−3.48 (m, 1H), 2.48 (d, J = 2.2 Hz, 1H), 1.10 (s, 9H), 0.93 (s, 9H). ^{13}C NMR ($CDCl_3$, 90 MHz) δ 158.2, 138.5, 136.9, 129.6, 129.4, 128.6, 128.5, 128.2, 128.0, 128.0, 127.4, 114.7, 81.6, 79.4, 75.3, 74.3, 72.7, 70.0, 68.3, 67.0, 27.5, 27.0, 22.6, 19.9. HRMS calcd for $C_{34}H_{48}NO_6Si$ $[M + NH_4]^+$ 594.3245, found 594.3238.

*(1R)-1,5-Anhydro-1-[4-(benzyloxy)phenyl]-3,4,6-tris-O-(2,2-dimethylpropanoyl)-D-galactitol (**4fa**). Epoxide **3f** Synthesis.* General procedure starting from **2f** (2.00 g, 5.02 mmol) and potassium monopersulfate (9.26 g, 15.1 mmol) in water (35.1 mL), acetone (5.5 mL), saturated sodium bicarbonate (50.2 mL), and dichloromethane (25.1 mL). **3f** was obtained as a white solid as a 10:1 mixture of two diastereomers (1.97 g, 95%). R_f 0.05 (70:30 heptane/ethyl acetate).

Epoxide Opening. General procedure using 4-benzyloxyiodobenzene (315 mg, 1.02 mmol), *n*-BuLi (380 μL, 25% w/w in heptane, 1.06 mmol), $ZnBr_2$−LiBr (0.96 mL, 32% w/w in *n*-Bu_2O, 1.06 mmol), and 1,2-anhydro-glucal **3f** (383 mg, 0.92 mmol). Purification by flash chromatography (95:5 heptane/ethyl acetate) afforded **4fa** as a colorless oil (292 mg, 53%). R_f 0.3 (95:5 heptane/ethyl acetate). ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.47−7.31 (m, 7H), 6.98 (d, J = 8.8 Hz, 2H), 5.53 (dd, J = 4.8, 3.7 Hz, 1H), 5.43 (dd, J = 6.6, 3.3 Hz, 1H), 5.15 (d, J = 3.3 Hz, 1H), 5.07 (s, 2H), 4.79 (dd, J = 12.1, 9.5 Hz, 1H), 4.29−4.22 (m, 1H), 4.17 (dd, J = 6.6, 2.9 Hz, 1H), 3.98 (dd, J = 12.1, 4.0 Hz, 1H), 2.16−1.86 (br s, 1H), 1.26 (s, 9H), 1.24 (s, 9H), 1.15 (s, 9H). ^{13}C NMR ($CDCl_3$, 90 MHz) δ 178.3, 177.5, 176.9, 158.4, 136.8, 128.6, 128.4, 128.0, 128.0, 127.5, 114.9, 71.7, 71.0, 70.1, 70.1, 70.0, 66.3, 38.9, 38.9, 38.7, 27.2, 27.1, 27.1. HRMS calcd for $C_{34}H_{50}NO_9$ $[M + NH_4]^+$ 616.3480, found 616.3477.

*(1R)-1,5-Anhydro-1-[4-(benzyloxy)phenyl]-4,6-O-(di-tert-butylsilanylidene)-3-O-(2,2-dimethylpropanoyl)-D-galactitol (**4ga**). Epoxide **3g** Synthesis.* General procedure starting from **2g** (179 mg, 0.48 mmol) and potassium monopersulfate (924 mg, 1.5 mmol) in water (3.4 mL), acetone (533 μL, 7.3 mmol), saturated sodium bicarbonate (4.8 mL), and dichloromethane (2.4 mL). **3g** was obtained as a white solid as a 20:1 mixture of two diastereomers (164 mg, 88%). R_f 0.05 (70:30 heptane/ethyl acetate).

Epoxide Opening. General procedure using 4-benzyloxyiodobenzene (261 mg, 0.84 mmol), *n*-BuLi (320 μL, 25% w/w in heptane, 0.88 mmol), $ZnBr_2$−LiBr (0.79 mL, 32% w/w in *n*-Bu_2O, 0.88 mmol), and 1,2-anhydro-glucal **3g** (296 mg, 0.50 mmol). Purification by flash chromatography (95:5 heptane/ethyl acetate) afforded **4ga** as a colorless oil (283 mg, 65%). R_f 0.3 (95:5 heptane/ethyl acetate). ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.69 (d, J = 8.8 Hz, 2H), 7.47−7.31 (m, 5H), 6.96 (d, J = 8.8 Hz, 2H), 5.30 (d, J = 6.2 Hz, 1H), 5.10 (d, J = 10.3, 3.3, 1H), 5.07 (s, 2H), 4.82−4.74 (m, 1H), 4.67 (d, J = 3.3 Hz, 1H), 4.16 (dd, J = 12.4, 2.2 Hz, 1H), 4.11 (dd, J = 12.4, 1.8 Hz, 1H), 3.41 (s, 1H), 2.24 (d, J = 4.4 Hz, 1H), 1.31 (s, 9H), 1.11 (s, 9H), 1.01 (s, 9H).^{13}C NMR ($CDCl_3$, 90 MHz) δ 178.4, 158.2, 136.9, 130.0, 128.9, 128.6, 127.9, 127.4, 114.7, 75.4, 73.4, 70.6, 69.9, 68.4, 67.8, 67.5, 39.1, 27.6, 27.3, 27.2, 23.3, 20.7. HRMS calcd for $C_{32}H_{50}NO_7Si$ $[M + NH_4]^+$ 588.3351, found 588.3339.

*(1R)-1,5-Anhydro-1-(3-{[5-(4-fluorophenyl)thiophen-2-yl]-methyl}-4-methylphenyl)-D-glucitol (**5**). Epoxide Opening.* General procedure using 2-(4-fluorophenyl)-5-(5-iodo-2-methylbenzyl)-thiophene (542 mg, 1.33 mmol), *n*-BuLi (500 μL, 25% w/w in heptane, 1.39 mmol), $ZnBr_2$−LiBr (1.20 mL, 32% w/w in *n*-Bu_2O, 1.39 mmol), and 1,2-anhydro-glucal **3g** (500 mg, 1.21 mmol). The crude mixture was evaporated to dryness and dissolved back in methanol (2.5 mL). After addition of sodium methoxide (5.25 mol/L in methanol, 0.23 mL, 1.0 equiv), the resulting mixture was heated at reflux overnight. The reaction was cooled down to room temperature followed by addition of acetic acid (76 μL, 1.1 equiv per hydroxyl group) and removal of the volatile materials. Purification by flash chromatography (1:30 methanol/DCM) afforded **5** as a white solid (295 mg, 55%). R_f 0.3 (95:5 heptane/ethyl acetate). ^{1}H NMR (DMSO-d_6, 600 MHz) δ 7.59 (dd, $J_{H-H,\ H-F}$ = 8.7, 5.9 Hz, 2H), 7.51 (s, 1H), 7.45 (d, J = 7.9 Hz, 1H), 7.27 (d, J = 3.4 Hz, 1H), 7.20 (t, J_{H-H} = J_{H-F} = 8.7 Hz, 2H), 7.11 (d, J = 7.9 Hz, 1H), 6.80 (d, J = 3.4 Hz, 1H), 5.15 (d, J = 5.3 Hz, 1H), 5.05 (d, J = 4.2 Hz, 1H), 4.91 (d, J = 5.3 Hz, 1H), 4.89 (d, J = 4.5 Hz, 1H), 4.83 (d, J = 3.4 Hz, 1H), 4.48−4.43 (m, 1H), 4.10 (s, 2H), 3.69−3.64 (m, 1H), 3.64−3.59 (m, 1H), 3.58−3.49 (m, 1H), 3.30−3.20 (m, 1H), 2.25 (s, 3H). ^{13}C NMR (DMSO-d_6, 150 MHz) δ 161.4 (d, J_{C-F} = 244.8 Hz), 143.7, 140.2, 137.6, 137.3, 134.1, 130.5 (d, J_{C-F} = 2.2 Hz), 129.6, 129.2, 126.9 (d, J_{C-F} = 7.7 Hz), 126.6, 126.3, 123.4, 115.9 (d, J_{C-F} = 22.0 Hz), 75.9, 73.5, 72.9, 72.7, 70.4, 60.8, 33.6, 18.7. HRMS calcd for $C_{24}H_{29}FNO_5S$ $[M + NH_4]^+$ 462.1745, found 462.1743.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01472.

^{1}H and ^{13}C NMR spectra of new compounds **4aa-4al** and **4ba-4ga** (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For recent reviews, see: Chao, E. C.; Henry, R. R. *Nat. Rev. Drug Discovery* **2010**, *9*, 551.

(2) (a) Ohtake, Y.; Sato, T.; Kobayashi, T.; Nishimoto, M.; Taka, N.; Takano, K.; Yamamoto, K.; Ohmori, M.; Yamaguchi, M.; Takami, K.; Yeu, S. Y.; Ahn, K. H.; Matsuoka, H.; Morikawa, K.; Suzuki, M.; Hagita, H.; Ozawa, K.; Yamaguchi, K.; Kato, M.; Ikeda, S. *J. Med. Chem.* **2012**, *55*, 7828. (b) Xu, G.; Lv, B.; Roberge, J. Y.; Xu, B.; Du, J.; Dong, J.; Chen, Y.; Peng, K.; Zhang, L.; Tang, X.; Feng, Y.; Xu, M.; Fu, W.; Zhang, W.; Zhu, L.; Deng, Z.; Sheng, Z.; Welihinda, A.; Sun, X. *J. Med. Chem.* **2014**, *57*, 1236. (c) Song, K.-S.; Lee, S. H.; Kim, M. J.; Seo, H. J.; Lee, J.; Lee, S.-H.; Jung, M. E.; Son, E.-J.; Lee, M. W.; Kim, J.; Lee, J. *ACS Med. Chem. Lett.* **2011**, *2*, 182. (d) Zhou, H.; Danger, D. P.; Dock, S. T.; Hawley, L.; Roller, S. G.; Smith, C. D.; Handlon, A. L. *ACS Med. Chem. Lett.* **2010**, *1*, 19. (e) Goodwin, N. C.; Mabon, R.;

DOI: 10.1021/acs.joc.5b01472
J. Org. Chem. 2015, 80, 9328−9335

Harrison, B. A.; Shadoan, M. K.; Almstead, Z. Y.; Xie, Y.; Healy, J.; Buhring, L. M.; DaCosta, C. M.; Bardenhagen, J.; Mseeh, F.; Liu, Q.; Nouraldeen, A.; Wilson, A. G. E.; Kimball, S. D.; Powell, D. R.; Rawlins, D. B. *J. Med. Chem.* **2009**, *52*, 6201.

(3) Ertugliflozin: (a) Bernhardson, D.; Brandt, T. A.; Hulford, C. A.; Lehner, R. S.; Preston, B. R.; Price, K.; Sagal, J. F.; Pierre, M. J., St; Thompson, P. H.; Thuma, B. *Org. Process Res. Dev.* **2014**, *18*, 57. (b) Bowles, P.; Brenek, S. J.; Caron, S.; Do, N. M.; Drexler, M. T.; Duan, S.; Dubé, P.; Hansen, E. C.; Jones, B. P.; Jones, K. N.; Ljubicic, T. A.; Makowski, T. W.; Mustakis, J.; Nelson, J. D.; Olivier, M.; Peng, Z.; Perfect, H. H.; Place, D. W.; Ragan, J. A.; Salisbury, J. J.; Stanchina, C. L.; Vanderplas, B. C.; Webster, M. E.; Weekly, R. M. *Org. Process Res. Dev.* **2014**, *18*, 66.

(4) Tofogliflozin: Ohtake, Y.; Sato, T.; Kobayashi, T.; Nishimoto, M.; Taka, N.; Takano, K.; Yamamoto, K.; Ohmori, M.; Yamaguchi, M.; Takami, K.; Yeu, S.; Ahn, K.; Matsuoka, H.; Morikawa, K.; Suzuki, M.; Hagita, H.; Ozawa, K.; Yamaguchi, K.; Kato, M.; Ikeda, S. *J. Med. Chem.* **2012**, *55*, 7828.

(5) Dapagliflozin: (a) Meng, W.; Ellsworth, B. A.; Nirschl, A. A.; McCann, P. J.; Patel, M.; Girotra, R. N.; Wu, G.; Sher, P. M.; Morrison, E. P.; Biller, S. A.; Zahler, R.; Deshpande, P. P.; Pullockaran, A.; Hagan, D. L.; Morgan, N.; Taylor, J. R.; Obermeier, M. T.; Humphreys, W. G.; Khanna, A.; Discenza, L.; Robertson, J. G.; Wang, A.; Han, S.; Wetterau, J. R.; Janovitz, E. B.; Flint, O. P.; Whaley, J. M.; Washburn, W. N. *J. Med. Chem.* **2008**, *51*, 1145. (b) Yu, Y.; Ji, Y. *Chin. J. Pharm.* **2011**, *2*, 42. (c) Deshpande, P. P.; Singh, J.; Pullockaran, A.; Kissick, T.; Ellsworth, B. A.; Jack, Z.; Gougoutas, J. Z.; Dimarco, J.; Fakes, M.; Reyes, M.; Lai, C.; Lobinger, H.; Denzel, T.; Ermann, P.; Crispino, G.; Randazzo, M.; Gao, Z.; Randazzo, R.; Lindrud, M.; Rosso, V.; Buono, F.; Wendel, W.; Doubleday, W. W.; Leung, S.; Richberg, P.; Hughes, D.; Washburn, W. N.; Meng, W.; Volk, K. J.; Mueller, R. H. *Org. Process Res. Dev.* **2012**, *16*, 577.

(6) Empagliflozin: Wang, X.-J.; Zhang, L.; Byrne, D.; Nummy, L.; Weber, D.; Krishnamurthy, D.; Yee, N.; Senanayake, C. H. *Org. Lett.* **2014**, *16*, 4090.

(7) (a) Lewis, M. D.; Cha, K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976. (b) Kraus, G. A.; Molina, M. T. *J. Org. Chem.* **1988**, *53*, 752. (c) Ellsworth, B. A.; Doyle, A. G.; Patel, M.; Caceres-Cortes, J.; Meng, W.; Deshpande, P. P.; Pullockaran, A.; Washburn, W. N. *Tetrahedron: Asymmetry* **2003**, *14*, 3243. (d) Deshpande, P. P.; Ellsworth, B. A.; Buono, F. G.; Pullockaran, A.; Singh, J.; Kissick, T. P.; Huang, M.-H.; Lobinger, H.; Denzel, T.; Mueller, R. H. *J. Org. Chem.* **2007**, *72*, 9746.

(8) Lemaire, S.; Houpis, I. N.; Xiao, T.; Li, J.; Digard, E.; Gozlan, C.; Liu, R.; Gavryushin, A.; Diène, C.; Wang, Y.; Farina, V.; Knochel, P. *Org. Lett.* **2012**, *14*, 1480.

(9) (a) Bellosta, V.; Czernecki, S. *J. Chem. Soc., Chem. Commun.* **1989**, 199. (b) Bellosta, V.; Czernecki, S. *Carbohydr. Res.* **1993**, *244*, 275.

(10) (a) Rainier, J. D.; Allwein, S. P. *J. Org. Chem.* **1998**, *63*, 5310. (b) Boulineau, F. P.; Wei, A. *Org. Lett.* **2002**, *4*, 2281. (c) Majumder, U.; Cox, J. M.; Rainier, J. D. *Org. Lett.* **2003**, *5*, 913. (d) Roberts, S. W.; Rainier, J. D. *Org. Lett.* **2005**, *7*, 1141.

(11) (a) Evans, D. A.; Trotter, B. W.; Côté, B. *Tetrahedron Lett.* **1998**, *39*, 1709. (b) Evans, D. A.; Trotter, B. W.; Coleman, P. J.; Côté, B.; Dias, L. C.; Rajapakse, H. A.; Tyler, A. N. *Tetrahedron* **1999**, *55*, 8671.

(12) (a) Rainier, J. D.; Cox, J. M. *Org. Lett.* **2000**, *2*, 2707. For applications in natural products synthesis, see: (b) Allwein, S. P.; Cox, J. M.; Howard, B. E.; Johnson, H. W. B.; Rainier, J. D. *Tetrahedron* **2002**, *58*, 1997. (c) Roberts, S. W.; Rainier, J. D. *Org. Lett.* **2007**, *9*, 2227.

(13) Parrish, J. D.; Little, R. D. *Org. Lett.* **2002**, *4*, 1439.

(14) Wipf, P.; Pierce, J. G.; Zhuang, N. *Org. Lett.* **2005**, *7*, 483.

(15) (a) Leeuwenburgh, M. A.; Timmers, C. M.; Van der Marel, G. A.; Van Boom, J. H.; Mallet, J. M.; Sinaÿ, P. G. *Tetrahedron Lett.* **1997**, *38*, 6251. (b) Xue, S.; Han, K.-Z.; He, L.; Guo, Q. X. *Synlett* **2003**, *6*, 870. (c) Cheng, G.; Fan, R.; Hernandez-Torres, J. M.; Boulineau, F. P.; Wei, A. *Org. Lett.* **2007**, *9*, 4849.

(16) Danishefsky, S. J.; Halcomb, R. L. *J. Am. Chem. Soc.* **1989**, *111*, 6661.

(17) (a) Mikula, H.; Svatunek, D.; Lumpi, D.; Glöcklhofer, F.; Hametner, C.; Fröhlich, J. *Org. Process Res. Dev.* **2013**, *17*, 313. (b) Taber, D. F.; DeMatteo, P. W.; Hassan, R. A. *Org. Synth.* **2013**, *90*, 350.

(18) Alberch, L.; Cheng, G.; Seo, S.-K.; Li, X.; Boulineau, F. P.; Wei, A. *J. Org. Chem.* **2011**, *76*, 2532.

(19) Cheshev, P.; Marra, A.; Dondoni, A. *Carbohydr. Res.* **2006**, *341*, 2714.

(20) See Supporting Information for the preparation of dry solutions of $ZnBr_2$·LiBr in *n*-dibutyl ether (around 100 ppm of water). Commercially available solutions containing around 1000 ppm of water gave lower yields.

(21) We have identified in some cases the migration of the pivaloyl residue from the 2- to the 3-hydroxy position.

(22) The addition of *n*-butyl zinc bromide to epoxide **2a** only gave traces of the desired alkyl *C*-glycoside by LC-MS.

(23) In this case, syn-selectivity was determined to be 98:2 after UPLC analysis of the crude mixture. In all other cases we were unable to detect significant proportions of the β-anomers, and we assume 98:2 is a representative ratio for the reaction in general.

(24) (a) Takahashi, Y.; Vasella, A. *Helv. Chim. Acta* **1992**, *75*, 1563. (b) Walvoort, M. T. C.; Kallemeijn, W. W.; Willems, L. I.; Witte, M. D.; Aerts, J. M. F. G.; Van der Marel, G. A.; Codée, J. D. C.; Overkleeft, H. S. *Chem. Commun.* **2012**, *48*, 10386. (c) Bucher, C.; Gilmour, R. *Angew. Chem., Int. Ed.* **2010**, *49*, 8724.

(25) Paquette, L. A.; Oplinger, J. A. *J. Org. Chem.* **1988**, *53*, 2953.

(26) Wehlan, H.; Dauber, M.; Mujica Fernaud, M. T.; Schuppan, J.; Keiper, S.; Mahrwald, R.; Juarez Garcia, M.-E.; Koert, U. *Chem. - Eur. J.* **2006**, *12*, 7378.

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